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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/556,454	Applicant(s) VOLLMER, TIMOTHY	
	Examiner MAURY AUDET	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant's amendment, adding new claims 26-29, and 105 page response are acknowledged.

As noted previously, the present application is a 371 National Stage entry of PCT/US04/15225, in which this Examiner also prepared both the Search & Written Reports (Forms 210 and 237 respectively) on the identical claims 1-25. The latter found that the invention, although finding Novelty under PCT Article 33(2), was not deemed to involve an Inventive Step under PCT Article 33(3). The findings therein, are transferred nearby verbatim via the US correlational Statutory Code section 35 USC 103.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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The invention is drawn to the composition and method of treating a subject afflicted with multiple sclerosis with the combination of active agents glatiramer acetate and mitoxantrone.

The rejection of claims 1-25 and new claims 26-29 under 35 U.S.C. 103(a) as being unpatentable over Szabo et al (US 6,531,464) in view of Arnon et al. (US 6,214,791) and Kerwar et al. (US 4,617,319), is maintained for the reasons of record. Applicant's arguments have been considered but are not found persuasive.

Applicant, in his 105 page response, including numerous MPEP sections and case law relevant to KSR/obviousness standards, essentially relies on MPEP section 2143.02, in his Section 5 Exhibit, which cites that:

2143.02 Reasonable Expectation of Success Is Required [R-6] -2100 Patentability

2143.02 Reasonable Expectation of Success Is Required [R-6]

A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. m, ~, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

I. OBVIOUSNESS REQUIRES ONLY A REASONABLE EXPECTATION OF SUCCESS

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (Claims directed to a method of treating depression with amitriptyline (or nontoxic salts thereof) were rejected as *prima facie* obvious over prior art disclosures that amitriptyline is a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess antidepressive properties, in

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view of prior art suggesting the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement and because a research paper comparing the pharmacological properties of these two compounds suggested clinical testing of amitriptyline as an antidepressant. The court sustained the rejection, finding that the teachings of the prior art provide a sufficient basis for a reasonable expectation of success.); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims were directed to a process of sterilizing a polyolefinic composition with high-energy radiation in the presence of a phenolic polyester antioxidant to inhibit discoloration or degradation of the polyolefin. Appellant argued that it is unpredictable whether a particular antioxidant will solve the problem of discoloration or degradation. However, the Board found that because the prior art taught that appellant's preferred antioxidant is very efficient and provides better

results compared with other prior art antioxidants, there would have been a reasonable expectation of success.).

II. AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED; APPLICANTS MAY PRESENT EVIDENCE SHOWING THERE WAS NO REASONABLE EXPECTATION OF SUCCESS

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success.); *In re O'Farrell*, 853 F.2d 894, 903,

7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

III. PREDICTABILITY IS DETERMINED AT THE TIME THE INVENTION WAS MADE

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Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986) (Although an earlier case reversed a rejection because of unpredictability in the field of monoclonal antibodies, the court found "in this case at the time this invention was made, one of ordinary skill in the art would have been motivated to produce monoclonal antibodies specific for human fibroblast interferon using the method of [the prior art] with a reasonable expectation of success." 3 USPQ2d at 1016 (emphasis in original).).

; to support his primary position, on page 4-5 of the response that:

"Yet furthermore, applicant has made the unexpected observation that immunosuppression with mitoxantrone accelerates and enhances the efficacy of glatiramer acetate administered to the patient (see instant claim 29; page 15, lines 15-18 of the subject application; and page 2, 2nd column, last full paragraph and page 7, 2nd column, last paragraph ending on page 8 of Vollmer et al.).

In addition, the enhancement of glatiramer acetate treatment is demonstrated by a significant reduction in both the accumulation of Gd-enhancing lesions and in the mean relapse rate (see instant claims 26-28 and Vollmer et al., page 5, bottom of 2nd column to page 6, 2nd column, first full paragraph).

The prior art provides no evidence or even suggestion that treatment with mitoxantrone would enhance the efficacy of glatiramer acetate in general or by reducing the accumulation of Gd-enhancing lesions or mean relapse rate."

The Examiner counters, based on Szabo et al.'s teaching of this combination from a list of 5 MS agents, that the presumption by one of ordinary skill in the art of using two known compounds for MS, in combination, is that 1 or the other would only enhance the other, and thereby provide some degree of additive, if not synergistic effect. Hence, the teachings of Szabo et al. in the first place, to even contemplate their combined therapeutic use for MS.

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Applicant on page 3 of the response attempts to disqualify Szabo et al.'s combination teaching, citing the Examiner's interpretation as erroneous; however, the Examiner counters that Applicant's Attorney has misinterpreted the "qualifying" language present in Szabo et al.

Applicant states:

Initially, the Examiner has misinterpreted claims 10 and 11 of Szabo et al. Specifically, these claims cannot be interpreted to disclose a combination treatment of glatiramer acetate and mitoxantrone. A proper construction of claim 11 indicates a disclosure of only one member of the group. This is well settled patent law. See, e.g. *Abbott Laboratories v. Baxter Pharmaceutical Products, Inc.*, 334 F.3d 1274, 1281, 67 USPQ2d 1191, 1196 (Fed. Cir.2003), attached hereto as Exhibit 1 holding that 'a' with 'consisting of' in this case indicates only one member of a Markush group. See *KJC Corp.*, 223 F.3d at 1356. If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim." **Claim 11 of Szabo et al. clearly fails to recite any qualifying language and, thus, clearly fails to support the Examiner's erroneous construction. In fact, claim 11 of Szabo et al. requires that no more than one member from the group is to be selected for administration.** Accordingly, the prior art fails to teach or suggest combining mitoxantrone and glatiramer acetate for treatment of multiple sclerosis.

Claims 10 and 11 of Szabo et al. expressly teach:

10. The method of claim 1, further comprising administering one or more additional agents for treating symptoms associated with multiple sclerosis.

11. The method of claim 10, wherein the second agent is selected from the group consisting of a glucocorticoid, an interferon, glatiramer acetate, immunoglobulin, and mitoxantrone.

The 5 "one or more additional agents" recited in claim 11 are the expressly contemplated one or additional agents. The 'or more' language removes Abbott as an analogous caselaw fact pattern

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because Szabo et al. must be read in light of itself and all claims to which it depends, which means the 'or more' does not somehow make the Markush group 'consisting of' language limited to only 1 agent.

Furthermore, as the second case cited, the 'or more' language IS the qualifying language that removes the present fact-pattern applying Szabo et al. from analogy with the KJC Corp. case that Applicant's Attorney has cited. Wherein, although the facts of KJC Corp were not fully provided the Examiner, it can only be presumed there was no such qualifying language latter, as is present in the Szabo et al. claim 10/11.

Applicant's Attorney is reminded that dependent claims are read as having ALL of the limitations of any claim to which they depend, thus the qualifying language of claim 10 to be read not separate from claim 11, but as fully encompassed by claim 11. Read this way, claim 11 actually reads:

11. The method of claim 1, further comprising administering one or more additional agents for treating symptoms associated with multiple sclerosis, wherein the second agent is selected from the group consisting of a glucocorticoid, an interferon, glatiramer acetate, immunoglobulin, and mitoxantrone.

Thus, the literal meaning of 'or more' in claim 11 (not 10), can only mean that the 'more' than 1 additional agent, must be selected from the group of 5 agents in claim 11. The fact that claim 11 recites this group of 5 (as 1 'or more' that may be coadministered) in proper Markush claim format using "consisting of" does not, as Applicant's Attorney has improperly interpreted the claim, mean that 'only 1' of those agents can be selected, based on the 'consisting of' language. If such were the case, this would contradict and cancel out the full scope of claim 11,

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and the breadth Issued Patentee in the claim 11, **that another 2 – 5 agents, the ‘or more’ than 1 claimed, is taught as contemplated for use in the composition thereof, for MS treatment –** depending on the symptoms being targeted, and the ability of 1 of more of those agents to target different or target better, certain symptoms of MS.

Continuing this thread, claim 10 and 11 claims that this ‘one or more additional agents are for treating symptoms associated with MS’. The reason there are many varied approach to the complex treatment of MS, is that there is no perfect therapy. It is well established that the 2 compounds presently claimed are capable of treating different symptoms of MS and/or the same symptoms but with different levels of success in individual patients – or 1 would trump the other as superior thereby eliminating the value of the other in the pharmaceutical market. Thus, the rationale for 'or more' in claim 10, is that the agents of claim 11 (or other nonclaimed agents) can be administered, based on the desired symptoms to be treated, or use thereof to treat certain symptoms better with one agent or another.

Combination therapy in highly complex disorders such as MS, or even diabetes, is well known in the art.

The Examiner has fully considered the record:

- 1) Applicant’s amendment and 105 page response;**
- 2) The Exhibits of Volmer’s 2008 article in MS; the MPEP section on 2143.02; the KSR and related caselaw;**
- 3) each in the context of the claimed invention in view of the prior art combination;**

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and can only conclude and maintain, not yet convinced by Applicant's arguments and evidence of record, that based the prior art combination, if not Szabo et al. alone, that one of ordinary skill in the art, using two known MS agents in combination (2 of 5 Szabo et al. taught/contemplated), would have had a reasonable expectation of success in treating MS by their combination, satisfying MPEP section 2143.02, as well as the recent case law guidance of and citing KSR.

The real, fundamental issue of the invention as claimed v. the prior art is whether Szabo et al. taught a laundry list of known MS agents that 'could' be selected for combinatorial therapy for MS, or small, "immediately envisaged" (borderline 102 art) for the same? The Examiner is not convinced by Applicant's evidence of record; however, voluminous it may be; that Applicant has removed the art to that of the former (laundry list) from that of what it appears to be (immediately envisaged). A list of 5 agents, and the express teaching (or at a minimum) that any of the 5 therein may be used concurrently in a combination therapy is simply too overwhelming evidence that such would have been predictable, in the form Applicant has presently claimed. Based on the predictable results that both agents presently claimed were known for use as MS treatment agents. Furthermore, Applicant's have claimed ANY form of administration of the two, "periodically" even (claim 1); including administering either agent "substantially preceding" the other (claims 16-17). Either of these limitations, under their broadest 'reasonable' interpretation, could mean days or even months apart of administration times, in combination or in the context of preceding the other. The breadth of this interpretation borders on indefiniteness in the context of what the metes and bounds of the invention really is, in order to carry out it's aim of reducing relapses of MS; and only further raises doubts as to a claimed

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invention directed to a therapy of known agents in combination for their known use, to somehow elicit something 'unexpected' (beyond merely synergistic effect, which would naturally be expected by administering two agents in combination, as Szabo et al. taught/suggested) - when the administration thereof is claimed essentially as "whenever" desired.

It is suggested that Applicant may wish to consider further review of any test data disclosed or evidence thereafter (e.g. via 1.132 Declaration) as to the metes and bounds of some specific amount/timeline regimen of both agents, that led Applicant's to believe they had stumbled upon a better combination therapy for those suffering from MS. Beyond the effect that would be expected by both known agents for their therapeutic benefit in MS sufferers, including beyond a mere synergistic effect.

The rejection is repeated below for continuity of record:

Szabo et al. teach “administering one or more additional agents for treating symptoms associated with multiple sclerosis”) of glatiramer acetate and mitoxantrone (claim 11, as two of only five specifically contemplated “additional agents” also capable of treating multiple sclerosis) (see entire document, especially claims 10-11).

Arnon et al. teach the use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (see entire document, especially claims 1 and 8; col. 1, lines 35-41; and Fig. 8).

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Kerwar et al. teach the use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (see entire document especially claim; col. 1; lines 5-9).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a combination composition comprising the active agents glatiramer acetate and mitoxantrone for the treatment of a subject afflicted with multiple sclerosis, in Szabo et al. because SZABO et al. teach administration of the combination (claim 10, i.e. “administering one or more additional agents for treating symptoms associated with multiple sclerosis”) of glatiramer acetate and mitoxantrone (claim 11, as two of only five specifically contemplated “additional agents” also capable of treating multiple sclerosis). ARNON et al. teach the use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (claims 1 and 8, col. 1, lines 35-41, and Fig. 8). KERWAR et al. teach the use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (claims, col. 1, lines 5-9). Based on the combination of references, it would have been predictable to one of ordinary skill in the art, at the time of the invention, to effectively administer the exclusive combination of glatiramer acetate and mitoxantrone, as primary agents (rather than only additional/secondary agents) for the treatment of multiple sclerosis in SZABO et al., because ARNON et al. teach the advantageous use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis and KERWAR et al. teach the advantageous use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MA, 9/22/09

/Maury Audet/
Examiner, Art Unit 1654
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